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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>A61K 31/47, 47/22</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 96/39143</b> <b>(43) International Publication Date:</b> 12 December 1996 (12.12.96)
<b>(21) International Application Number:</b> PCT/EP96/02438 <b>(22) International Filing Date:</b> 4 June 1996 (04.06.96) <b>(30) Priority Data:</b> 08/461,385                      5 June 1995 (05.06.95)                      US <b>(71) Applicants (for all designated States except US):</b> BION-UMERIK PHARMACEUTICALS, INC. [US/US]; Suite 1250, 8122 Datapoint Drive, San Antonio, TX 78229 (US). LUCAS, Brian, Ronald [GB/GB]; 135 Westhall Road, Warlingham, Surrey CR6 9HJ (GB). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> HAUSHEER, Frederick, Herman [US/US]; 129 Aylesbury Hill, San Antonio, TX 78209 (US). MURALI, Dhanabalan [IN/US]; Apartment 5907, 11146 Vance Jackson, San Antonio, TX 78230 (US). HARIDAS, Kochat [IN/US]; Apartment 2208, 5700 North Knoll, San Antonio, TX 78240 (US). REDDY, Dasharatha, Gauravaram [IN/US]; Apartment 4201, 4400 Horizon Hill Boulevard, San Antonio, TX 78229 (US). <b>(74) Agent:</b> LUCAS, Brian, Ronald; 135 Westhall Road, Warlingham, Surrey CR6 9HJ (GB).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> PHARMACEUTICAL FORMULATIONS OF HIGHLY LIPOPHILIC CAMPTOTHECIN DERIVATIVES		
<b>(57) Abstract</b>  A pharmaceutical formulation, as a solution or suspension of pH from 2 to 6, of camptothecin or a lipophilic camptothecin derivative, having a water solubility of less than 5 micrograms/ml, in N-methylpyrrolidin-2-one.		

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PHARMACEUTICAL FORMULATIONS OF HIGHLY LIPOPHILIC  
CAMPTOTHECIN DERIVATIVES

Field of the Invention

5        This invention relates to useful, novel and non-obvious formulations of camptothecin derivatives, and will have particular application to formulations of poorly water soluble (<5µg/ml) camptothecin derivatives.

10      Background of the Invention

For the purpose of this invention, poorly water soluble and highly lipophilic camptothecin derivatives (referred to as "HLCD" for the purposes of this invention) are defined interchangeably as any unsubstituted  
15      or any A-ring and/or B-ring substituted camptothecin which has a water solubility of less than 5 micrograms per milliliter (<5µg/ml) of water. Also for the purposes of the instant invention, the terms "highly lipophilic" and "poorly water soluble" are used interchangeably to  
20      describe the fundamental bioavailability and chemical behaviour of the camptothecin derivatives.

Utilizing HPLC and NMR techniques, researchers have demonstrated that camptothecin and many of its derivatives undergo an alkaline, pH-dependent hydrolysis of  
25      the E-ring lactone. The slow reaction kinetics allow one to assess whether both the lactone and non-lactone forms of the drug stabilize the topoisomerase I-cleaved DNA complex. Studies indicate that only the closed lactone form of the drug helps stabilize the cleavable  
30      complex. This observation provides reasoning for the high degree of drug activity observed in solid tumor models. Tumor cells, particularly hypoxic cells prevalent in solid neoplasms, have relatively lower intracellular pH levels than normal cells. At pH levels  
35      below 7.0, the lactone E-ring form of camptothecin

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predominates.

Formulations of camptothecin and its derivatives in the lactone form are difficult to prepare, due to the factors cited above. The poor solubility of these compounds in aqueous solution prohibits administration of effective doses. The opening of the lactone ring in alkaline formulations precludes their utility as well, due to a substantial reduction in the anti-tumor potency of the compounds.

10 The prior art teaches the use of various organic solvents useful for camptothecin formulations. This prior art is identified in the Information Disclosure Statement accompanying this application. Such solvents include lipid-based oils, such as cottonseed oil, peanut  
15 oil, IL-20 and others, and organic solvents such as N,N-dimethylacetamide (DMA), dimethylisosorbide (DMI), and others. Solubility of the compounds in lipid-based solvents is generally less than 1mg/ml, while the solubility increases to as high as about 6.7mg/ml in certain  
20 organic solvents.

#### Summary of the Invention

The formulations of this invention include as the primary solvent the compound N-methylpyrrolidin-2-one, also referred to as N-methylpyrrolidinone, or simply, NMP. The solubility of highly lipophilic, poorly water soluble camptothecin derivatives is increased to between 15.0 and 20.0mg/ml in NMP, which allows for much more concentrated solutions to be prepared in advance of  
25 formulating. The resulting higher drug concentration attained by the instant invention allows greater utility for preparing oral and parenteral formulations.

The preferred formulations of this invention include the following: (a) HLCD; (b) NMP; (c) polyethylene glycol (PEG) or propylene glycol; (d) an acid; (e) a  
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non-ionic surfactant; and (f) a low MW alcohol. In addition, certain formulations may also include (g) a heavy oil, such as epoxylated castor oil; (h) glycerol; and (i) taurocholic acid or a pharmaceutically acceptable salt thereof, or a similar intestinal absorption enhancing agent.

The solutions and formulations of this invention are able to contain a high concentration of effective ingredient due to the unpredictably high solubility of the compounds in NMP. This allows a lower solvent volume delivery to the patient to deliver the same amount of effective ingredient, which in turn results in reduced risk of toxicity and greater patient acceptance.

The formulations of this invention can be tailored for various types of delivery, including parenteral, subcutaneous and oral, among others. Specific examples of oral and parenteral formulations are given in the description of the preferred embodiments which follows.

#### 20 Description of the Preferred Embodiments

The preferred formulations disclosed below are not intended to be exhaustive or to limit the invention to the precise forms disclosed. Rather, they have been chosen and described to explain the principles of the invention, and their application and practical use to best enable others skilled in the art to follow its teachings.

The pharmaceutical formulations which comprise this invention include as basic ingredients, a pharmaceutically effective amount of a highly lipophilic camptothecin derivative (HLCD) dissolved or suspended in N-methylpyrrolidin-2-one (NMP). The solubility of most HLCDs in NMP is between 15.0 and 20.0mg/ml. In formulating solutions it is desirable to use enough NMP to completely dissolve the HLCD prior to adding any other

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excipients or diluents. Approximate ratios for formulating solutions are between 25 parts by weight to 1,000 parts by weight NMP per part by weight of HLCD, preferably between 50 to 500 parts by weight NMP per part HLCD, and most preferably between 100 to 300 parts by weight NMP per part HLCD. In the most preferred case, this will yield an initial NEAT solution concentration of about 1mg/ml to about 40mg/ml.

Suspensions, typically employed in orally administered formulations, may include significantly higher concentrations, up to 400mg/ml of the NEAT formulation.

Other pharmaceutically acceptable diluents and excipients may also be included in the preferred formulations, as outlined below. Typically, a pharmaceutical formulation of HLCD will include from 1.0 to 40.0 mg of HLCD per ml of solution or 1mg/ml to 400mg/ml suspension.

The pharmaceutically acceptable excipients and diluents preferably will be chosen from the following groups, keeping in mind that the exact nature of the formulation will depend upon the intended method of delivery.

One of the pharmaceutically acceptable excipients included in the formulation is a pharmaceutically acceptable acid, which is included to lower the pH of the formulation to between 2.0-6.0 (most preferably between 3.0-5.0) to keep the HLCD in its active lactone configuration. The preferred acid may be chosen from any one of a number of pharmaceutically acceptable mineral acids or organic acids, including hydrochloric acid, phosphoric acid, tartaric acid, lactic acid, ascorbic acid, citric acid, gluconic acid, fumaric acid, maleic acid and others. The acid will preferably be employed at the ratio of 10 to 5,000 parts by weight of the HLCD, most preferably between 100 to 2,500 parts by weight per part

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of HLCD. Citric acid is the most preferred acid.

Other excipients will include polyethylene glycol (PEG) or propylene glycol, and a non-ionic surfactant. The preferred PEG has a molecular weight of 300 to 400, most preferably 300 for parenteral formulations and 400 for oral formulations. PEG is included in the formulation at a ratio of between 100 to 10,000 parts by weight of PEG to each part by weight HLCD.

The preferred surfactant is a polysorbate-based compound, most preferably polysorbate-80 (PSB-80). The surfactant is included in the formulation at a range of 100 to 10,000 parts by weight of PSB to each part by weight HLCD. Most preferably the ratio is between 250 and 6500 parts by weight PSB per part of HLCD.

Parenteral formulations can optionally include a quantity of a lower alcohol, most preferably ethyl alcohol and/or benzyl alcohol, and a lipid based excipient, preferably castor oil, most preferably an epoxylated castor oil such as Cremaphor-80.

The lower alcohol is incorporated into the formulation at between 0 to 5,000 parts by weight of each alcohol used per part by weight HLCD, with the maximum alcohol content being 10,000 parts by weight alcohol per part by weight of HLCD.

Lipid based excipient (Cremaphor-80) is incorporated into the formulation at between 0 to 10,000 parts by weight per part of HLCD.

Oral formulations will include the above ingredients and may optionally include a quantity of glycerol. Preferred ratio of glycerol is 0 to 5 parts by weight glycerol per part by weight of HLCD, most preferably 0.5 to 2.5 parts by weight per part by weight HLCD.

Oral formulations may further include an intestinal absorption facilitating compound, most preferably a bile acid such as taurocholic acid or a salt thereof at from



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1 to 10 parts by weight per part by weight of HLCD. Oral formulations are also preferably formulated and incorporated into a pharmaceutically acceptable carrier, such as soft or hard gelatin capsules, among others, to facilitate swallowing.

Table 1 below illustrates a typical pharmaceutical-ly acceptable formulation of HLCD/NMP adapted for parenteral administration to a patient.

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TABLE 1  
COMPONENT PARTS FOR  
PARENTERAL FORMULATIONS OF HLCD

15	Ingredients	pts by wt
	HLCD	1 (1-40mg/ml)
	Ethyl Alcohol	0 to 5,000
	Benzyl Alcohol	0 to 5,000
20	Acid	100 to 5,000
	PEG 400	100 to 10,000
	NMP	25 to 10,000
	Cremaphor-EL	100 to 10,000
25	Glycerol	0 to 2.5
	Taurocholic Acid	0 to 10
	Polysorbate 80 (Tween-80)	100 to 10,000

30 Parenteral formulations are typically diluted with a common delivery solution such as 5% dextrose USP, lactated Ringer's solution or aqueous saline prior to administration to the patient.

Preferred oral formulations of HLCD/NMP are illustrated in Table 2.

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TABLE 2  
COMPONENT PARTS FOR ORAL FORMULATION  
OR HLCD

5	Ingredients	pts by wt
	HLCD	1 (1-400mg/ml)
	NMP	25 to 1,000
10	Citric Acid	100 to 5,000
	EtOH	100 to 5,000
	Polysorbate-80 (Tween-80)	100 to 10,000
	PEG-400	100 to 10,000
15	Glycerin	1.5 to 2.5
	Taurocholic Acid	1 to 10

20 Oral formulations are preferably encapsulated in a suitable carrier for oral delivery, typically gelatin capsules.

Preferred HLCD's used as active ingredients in the above formulations include camptothecin (CPT) and its derivatives which have a solubility of less than 5  
25 micrograms per millileter of water. Included in this group are CPT derivatives which have substitutions at one or more of the following positions on the molecule: (a) 7-substitutions; (b) 9-substitutions; (c) 10-substitutions; and (d) 11-substitutions; or any combina-  
30 tion of the above in a di- or tri-substituted CPT derivative having a solubility of <5µg/ml in water. Most preferred derivatives of CPT which fit into the category of HLCD are 10,11-methylenedioxy camptothecin, 10,11-ethylenedioxy camptothecin, 7-ethyl camptothecin, 7-  
35 ethyl-10-hydroxy camptothecin, 9-methyl camptothecin, 9-

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chloro-10,11-methylenedioxy camptothecin, 9-chloro camptothecin, 10-hydroxy camptothecin, 9,10-dichloro camptothecin, 10-bromo camptothecin, 10-chloro camptothecin, 9-fluoro camptothecin, 10-methyl camptothecin, 10-fluoro camptothecin, 9-methoxy camptothecin, 9-chloro-7-ethyl CPT, and 11-fluoro camptothecin. Other HLCDs will also fit the profile for the most preferred active compounds and their inclusion into these formulations can be achieved with a minimum amount of experimentation.

The following specific examples illustrate the most preferred formulations which constitute this invention. These formulations are included to illustrate the best modes of making the formulations are not introduced to limit the invention in any way.

#### Examples 1 and 2

##### Solubility of CPT and 7-ethyl CPT in NMP

(1) A mixture of CPT (14mg) and NMP (1ml) was sonicated in a clean vial at 50 degrees Celsius for 30 minutes. The solution appeared clear and no precipitation or cloudiness appeared even after 72 hours at ambient temperature.

(2) A mixture of 7-ethyl CPT (11.5mg) and NMP (0.5ml) was sonicated in a clean vial at 50 degrees Celsius for 30 minutes. The solution appeared clear and no precipitation or cloudiness appeared even after 1 week at ambient temperature.

#### Examples 3 and 4

The Following NMP Formulations were Prepared

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Formulation #1

Ethanol	6.4ml
Citric Acid	1.0g
PEG 300	50g
NMP	10.7ml
TWEEN 80	10g

The above ingredients were mixed in the above order. First citric acid was dissolved in ethanol by sonication at 50 degrees Celsius for 30 minutes.

Formulation #2

Ethanol	20.3ml
Benzyl Alcohol	3.44ml
Citric Acid	4.0g
PEG 300	40g
NMP	8.55ml
TWEEN 80	8.0g

The above ingredients were mixed in the above order. First citric acid was dissolved in ethanol by sonication at 50 degrees Celsius for 30 minutes.

Example 3: Solubility of CPT in Formulation #1

Solutions of CPT in above Formulation #1 were prepared at concentrations of 0.3, 0.4, and 0.5mg of CPT in 1ml of formulation. The mixtures were sonicated at 50 degrees Celsius for 60 min. There were no cloudiness, suspension or precipitation. The mixtures were filtered through 0.2 micron filter. The mixtures were diluted with 0.9% sodium chloride solution and studied

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for the appearance of Tyndall effect as given in the following tables:

Table 1: CPT 0.3mg/ml of formulation #1, with dilution by 0.9% NaCl solution

Dilution	0 min	15 min	30 min	45 min	60 min	90 min	120 min	1 day
1:1	clear	clear	clear	clear	clear	clear	clear	---
1:2	clear	clear	clear	clear	clear	clear	clear	---
1:5	clear	clear	clear	clear	clear	clear	clear	---
1:10	clear	clear	clear	clear	clear	clear	clear	---
1:100	clear	clear	clear	clear	clear	clear	clear	clear

Table 2: CPT 0.4mg/ml of formulation #1, with dilution by 0.9% NaCl solution

Dilution	0 min	15 min	30 min	45 min	60 min	90 min	120 min	1 day
1:1	clear	clear	clear	clear	clear	clear	clear	---
1:2	clear	clear	clear	clear	clear	clear	clear	---
1:5	clear	clear	clear	clear	clear	clear	clear	---
1:10	clear	clear	---	---	---	---	---	---
1:100	clear	clear	clear	clear	clear	clear	clear	clear

Table 3: CPT 0.5mg/ml of formulation #1, with dilution by 0.9% NaCl solution

Dilution	0 min	15 min	30 min	45 min	60 min	90 min	120 min	1 day
1:1	clear	clear	clear	clear	clear	clear	---	---
1:2	clear	clear	clear	clear	clear	---	---	---
1:5	clear	clear	clear	clear	---	---	---	---
1:10	clear	clear	---	---	---	---	---	---
1:100	clear	clear	clear	clear	clear	clear	clear	clear

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**Example 4: Solubility of 7-ethyl CPT in Formulation #1**

Solutions of 7-ethyl CPT in above Formulation #1 were prepared at concentrations of 0.5, 0.6, 0.7 and 1.0mg of 7-ethyl CPT in 1ml of formulation. The mixtures were sonicated at 50 degrees Celsius for 60 min. There were no cloudiness, suspension or precipitation. The mixtures were filtered through 0.2 micron filter. The mixtures were diluted with 0.9% sodium chloride solution and studied for the appearance of Tyndall effect as given in the following tables:

Table 4: 7-ethyl CPT 0.5mg/ml of formulation #1, with dilution by 0.9% NaCl solution

Dilution	0 min	15 min	30 min	45 min	60 min	90 min	120 min	1 day
1:1	clear	clear	clear	clear	clear	clear	clear	clear
1:2	clear	clear	clear	clear	clear	clear	clear	clear
1:5	clear	clear	clear	clear	clear	clear	clear	clear
1:10	clear	clear	clear	clear	clear	clear	clear	clear
1:100	clear	clear	clear	clear	clear	clear	clear	clear

Table 5: 7-ethyl CPT 0.6mg/ml of formulation #1, with dilution by 0.9% NaCl solution

Dilution	0 min	15 min	30 min	45 min	60 min	90 min	120 min	1 day
1:1	clear	clear	clear	clear	clear	clear	clear	clear
1:2	clear	clear	clear	clear	clear	clear	clear	clear
1:5	clear	clear	clear	clear	clear	clear	clear	clear
1:10	clear	clear	clear	clear	clear	clear	clear	clear
1:100	clear	clear	clear	clear	clear	clear	clear	clear

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Table 6: 7-ethyl CPT 0.7mg/ml of formulation #1, with dilution by 0.9% NaCl solution

Dilution	0 min	15 min	30 min	45 min	60 min	90 min	120 min	1 day
1:1	clear	clear	clear	clear	clear	clear	clear	clear
1:2	clear	clear	clear	clear	clear	clear	clear	clear
1:5	clear	clear	clear	clear	clear	clear	clear	clear
1:10	clear	clear	clear	clear	clear	clear	clear	clear
1:100	clear	clear	clear	clear	clear	clear	clear	clear

Table 7: 7-ethyl 1.0mg/ml of formulation #1, with dilution by 0.9% NaCl solution

Dilution	0 min	15 min	30 min	45 min	60 min	90 min	120 min	1 day
1:1	clear	clear	clear	clear	clear	clear	clear	clear
1:2	clear	clear	clear	clear	clear	clear	clear	---
1:5	clear	clear	clear	clear	clear	clear	clear	---
1:10	clear	clear	---	---	---	---	---	---
1:100	clear	clear	clear	clear	clear	clear	clear	clear

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CLAIMS

1. A pharmaceutical formulation, as a solution or suspension of pH from 2 to 6, of camptothecin or a lipophilic camptothecin derivative, having a water solubility of less than 5 micrograms/ml, in N-methylpyrrolidin-2-one.
2. A formulation according to Claim 1, further including one or more pharmaceutically acceptable excipients.
3. A formulation according to Claim 2, wherein the excipient(s) are polyethylene glycol, epoxylated castor oil, an aliphatic alcohol of 1 to 4 carbon atoms or benzyl alcohol.
4. A formulation according to Claim 3, wherein the aliphatic alcohol is ethanol.
5. A formulation according to Claim 1, 2, 3 or 4, further including taurocholic acid or a pharmaceutically acceptable salt thereof.
6. A formulation according to Claim 1, 2, 3, 4 or 5, further including a non-ionic surfactant.
7. A formulation according to Claim 1, 2, 3, 4, 5 or 6, wherein the concentration of the camptothecin or derivative thereof is from 1.0 mg/ml to the solubility or suspendibility limit.
8. A formulation according to Claim 1, 2, 3, 4, 5 or 6, wherein the camptothecin derivative is a 7-ethyl, 7-ethyl-10-hydroxy, 10,11-methylenedioxy, 10,11-ethylenedioxy, 9-methyl, 9-chloro-10,11-methylenedioxy, 9-chloro, 10-hydroxy, 9,10-dichloro, 10-bromo, 10-chloro, 9-fluoro, 10-methyl, 10-fluoro, 9-methoxy, 9-chloro-7-ethyl or 11-fluoro derivative.
9. A formulation according to Claim 1, comprising the following components in proportions lying within the following ranges, all weight/weight of the camptothecin or derivative thereof:
  - a) 25-1,000 parts of N-methylpyrrolidin-2-one,



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- b) 100-5,000 parts of a pharmaceutically acceptable acid,
  - c) 0-10 parts of a taurocholic acid or a pharmaceutically acceptable salt thereof,
  - 5 d) 0-2.5 parts of glycerol,
  - e) 100-10,000 parts of polyethylene glycol,
  - f) 100-5,000 parts of an aliphatic alcohol having 1 to 4 carbon atoms or benzyl alcohol,
  - g) 100-10,000 parts of a non-ionic surfactant,
  - 10 h) 0-10,000 parts of epoxylated castor oil.
10. A formulation according to Claim 9 diluted with a pharmaceutically acceptable diluent to form a deliverable solution, wherein the concentration of the camptothecin or derivative thereof is from 0.001 to 1.0 mg/ml.

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# INTERNATIONAL SEARCH REPORT

Intn. Application No

PCT/EP 96/02438

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 A61K31/47 A61K47/22

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>PHARM. RES., vol. 10, no. 10(suppl.), 1993, UNIV. PITTSBURGH, ABBOTT (PITTSBURGH, PENNSYLVANIA, NORTH CHICAGO, ILLINOIS, USA, page 269 XP000579393 N.G. DAS ET AL.: "solubilization and enhanced transport kinetics of camptothecin from submicron O/w emulsions" * cf. abstract*</p> <p style="text-align: center;">---</p> <p style="text-align: center;">-/--</p>	1-10

☒ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

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Date of the actual completion of the international search

3 September 1996

Date of mailing of the international search report

13.09.96

Name and mailing address of the ISA

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Authorized officer

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# INTERNATIONAL SEARCH REPORT

Inter. Appl. No.  
PCT/EP 96/02438

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>PROC. AM. ASSOC. CANCER RES., vol. 34, March 1993, 84TH ANN. MEETING IN ORLANDO, FLORIDA, pages 422-no 2519, XP000578376 SUGARMAN S. ET AL.: "liposomal camptothecin: formulation and cytotoxicity against kb cells." *cf. abstract*</p>	1-10
P,A	<p>--- PROC. AM ASSOC. CANCER RES., vol. 37, March 1996, 87TH ANN. MEETING, WASHINGTON, DC, pages 293-no1992, XP000578172 K. MICHAELS ET AL.: "intratumoral delivery of topo I and topo II inhibitors in aqueous and anhydrous delivery vehicle (adv) systems: focus on camptothecin and azatoxins" *cf. abstract*</p> <p>-----</p>	1-10

## MERCHANT & GOULD

### REQUEST FOR PLANNED TIME OFF/COMP TIME

#### To be completed by Employee

Name: Judy Schmidt

Date: December 13, 2001

Dates/Hours Requested: Friday, December 21, 2001 -- leaving  
at 12:00 noon

☒ PTO

☐ Comp Time (max 3.75 hours in same work week)

Work Assignment: Anna Manville and John Gould

All my docketing correspondence has been or will be:

☒ completed ☐ coordinated with secretarial coordinator

\_\_\_\_\_  
Employee Signature

#### To be completed by Attorney/Supervisor

I acknowledge that the above-named person will be out of the office on the dates indicated.

I ☐ will not need assistance during the absence.

I ☐ will need assistance during the absence as indicated below:

\_\_\_\_\_  
\_\_\_\_\_

\_\_\_\_\_  
Attorney/Supervisor

\_\_\_\_\_  
Attorney/Supervisor

#### To be completed by Human Resources Department

Time off has been ☐ Approved ☐ Not Approved

Name: \_\_\_\_\_

Date: \_\_\_\_\_

### NOTIFICATION OF UNPLANNED TIME OFF

#### To be completed by Employee

Date(s) Absent: \_\_\_\_\_

Total Hours: \_\_\_\_\_

I am electing to use \_\_\_\_\_ hours from my Extended Illness Bank.

\_\_\_\_\_  
Employee Signature